

**Amendments to the Claims:**

The listing of claims will replace all prior version, and listings, of claims in the application:

**Listing of Claims:**

1. (Previously Presented) A method for identifying constitutively activating mutations in an orphan receptor or an ion channel, comprising:
  - (a) identifying small or medium side-chain amino acid residues of a candidate orphan receptor that are located in or proximate to a transmembrane segment of the orphan receptor;
  - (b) providing a library of coding sequences for potentially activating mutations of the candidate orphan receptor or ion channel, which library is generated by replacing only coding sequences for the identified small or medium side-chain amino acids with coding sequences for large side-chain amino acids, wherein the mutation is conservative with respect to charge;
  - (c) expressing the library in mammalian host cells;
  - (d) measuring the activity of the encoded receptor or ion channel in the mammalian host cells; and
  - (e) identifying those coding sequence(s) which encoded activated receptors or ion channels.

Claims 2-3 (Canceled)

4. (Original) The method of claim 1, wherein the receptor is a multipass transmembrane receptor.
5. (Original) The method of claim 4, wherein the receptor is a 7TM receptor selected from the group consisting of: a G-protein coupled receptor, a chemoattractant peptide receptor,

a neuropeptide receptor, a light receptor, a neurotransmitter receptor, and a polypeptide hormone receptor.

Claims 6-7 (Canceled)

8. (Original) The method of claim 1, wherein the activity is measured directly by determining the level of second messengers generated in response to receptor or ion channel activation.
9. (Previously Presented) The method of claim 1, wherein the activity is measured indirectly by determining the level of transcription from an indicator gene.
10. (Original) The method of claim 9, wherein the indicator gene is an unmodified endogenous gene.
11. (Original) The method of claim 9, wherein the indicator gene is a heterologous reporter gene, the activation of the transcriptional regulatory element of which is directly or indirectly regulated by the receptor or ion channel.
12. (Original) The method of claim 10 or 11, wherein the level of transcriptional activation of the indicator gene is amplified by overexpressing one or more intermediate components of the signaling cascade leading to the activation of the indicator gene.
13. (Original) The method of claim 9, wherein the sensitivity of the indicator gene is modified by manipulating the promoter sequence at the natural locus for the indicator gene.
14. (Original) The method of claim 9, wherein the activity of the indicator gene is modified by manipulating the transcriptional regulatory sequence at the natural locus for the indicator gene.

15. (Original) The method of claim 9, wherein the activity of the indicator gene is modified by replacing the transcriptional regulatory sequence of the endogenous indicator gene with that of a heterologous gene.
16. (Original) The method of any one of claim 11, 14, or 15, wherein the transcriptional regulatory element is derived from that of immediate early genes.
17. (Original) The method of any one of claim 11, 14, or 15, wherein the transcriptional regulatory element is derived from several heterologous genes.
18. (Original) The method of claim 11, wherein the reporter gene encodes a gene product selected from the group consisting of: chloramphenicol acetyl transferase, beta-galactosidase, secreted alkaline phosphatase, a gene product which confers a growth signal, and a gene product for growth in media containing aminotriazole or canavanine.
19. (Original) The method of claim 1, wherein the small or medium side-chain amino acids are located at the interfaces between transmembrane helices.
20. (Original) The method of claim 1, wherein the small or medium side-chain amino acids are selected from the group consisting of: glycine, alanine, and serine.
21. (Original) The method of claim 1, wherein the small or medium side-chain amino acids are selected from the group consisting of: asparagine, aspartic acid, cysteine, proline, threonine and valine.
22. (Original) The method of claim 1, wherein the large/bulky side-chain amino acids are selected from the group consisting of: tryptophane, leucine, histidine, threonine, and tyrosine.

23. (Original) The method of claim 1, wherein the large side-chain amino acids are selected from the group consisting of: asparagine, cysteine, glutamine, isoleucine, methionine, phenylalanine, proline, and valine.

Claims 24-27 (Canceled).

28. (Previously Presented) The method of claim 1, wherein the cell is a pigment cell capable of dispersing or aggregating its pigment in response to an activated receptor or ion channel.

29. (Original) The method of claim 1, wherein the mutation is identified as an activating mutation if the activity of the mutant polypeptide increases by at least 2-fold when compared to the activity of the wild-type polypeptide.

30. (Original) The method of claim 1, wherein the mutation is identified as an activating mutation if the activity of the mutant polypeptide increases by at least 5-fold when compared to the activity of the wild-type polypeptide.

31. (Original) The method of claim 1, wherein the mutation is identified as an activating mutation if the activity of the mutant polypeptide increases by at least 10-fold when compared to the activity of the wild-type polypeptide.

32. (Previously Presented) A method for identifying constitutively activating mutations in an orphan multipass transmembrane receptor, comprising:

- (a) identifying small or medium side-chain amino acid residues of a candidate orphan multipass transmembrane receptor that are located in or proximate to a transmembrane segment of the receptor;
- (b) providing a library of coding sequences for the multipass transmembrane receptor, which library includes variant sequences which differ from the wild-type sequence of the receptor by one or more point mutations at only the identified amino acid residues from (a), wherein the mutations are conservative with respect

In re Application Of:  
Beachy and Taipale  
Application No.: 09/943,641  
Filed: August 30, 2001  
Page 6

PATENT  
Attorney Docket No. JHU1970-1

to charge;

- (c) expressing the library in mammalian host cells;
- (d) measuring the activity of the encoded multipass transmembrane receptor in the mammalian host cells; and
- (e) identifying those coding sequence(s) which encoded activated multipass transmembrane receptor.

Claims 33-52 (Canceled)